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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,625	02/26/2004	Naoya Tsurushita	149 US UT01	6526

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PDL BIOPHARMA, INC.
Attn: Legal Department
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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
11/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,625	TSURUSHITA ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30,32 and 36-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,32 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 17 August 2007 has been entered.

2. Claims 1-29, 31 and 33-35 are canceled.
Claims 30 and 32 have been amended.
Claims 36-39 have been added.

3. Claims 30-33 are under consideration.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections/Rejections Withdrawn

5. The rejection of claim 32 under 35 U.S.C. 112, second paragraph, for insufficient antecedent basis for the limitation "the amino acid of the human acceptor immunoglobulin framework..." is withdrawn in view of the amendments to the claim.

6. The rejection of claims 30-33 under 35 U.S.C. 103(a) as being unpatentable over Andris-Widhopf et al (Journal of Immunological Methods, 242:159-181, 2000) and Queen et al (U.S. Patent 5,530,101, issued 6/25/1996, IDS reference A1 filed 1/10/05) is withdrawn in view of the amendments to the claims and the cancellation of claim 32.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 30, 32 and 36-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 8/17/2007 has introduced NEW MATTER into the claims. Claim 30 as presently amended recites wherein a residue in at least one position selected from the group consisting of H78, H93, L66 and L69 of the human acceptor framework is replaced with the corresponding amino acid from the donor chicken immunoglobulin according to Kabat numbering and newly added claims 36-39 recite wherein the residue is H78, wherein the residue is H93, wherein the residue is L66 and wherein the residue is L69, respectively. Thus, the claims encompass a variety of subgenera of humanized chicken immunoglobulins wherein at least one residue selected from the group consisting of H78, H93, L66 and L69 is replaced with the corresponding residue of the chicken immunoglobulin, a subgenus of humanized chicken immunoglobulins wherein residue H78 is replaced with the corresponding residue of the chicken immunoglobulin, a subgenus of humanized chicken immunoglobulins wherein residue H93 is replaced with the corresponding residue of the chicken immunoglobulin, a subgenus of humanized chicken immunoglobulins wherein residue L66 is replaced with the corresponding residue of the chicken immunoglobulin, and a subgenus of humanized chicken immunoglobulins wherein residue L69 is replaced with the corresponding residue of the chicken immunoglobulin. The response filed 8/17/2007 points to original claim 33 (e.g., claims filed 2/26/2004) for support of newly added claims 36-39. This has been fully considered but is not found persuasive. Original claim 33 recites wherein a residue in at least one position selected from the group consisting of H67, H78, H93, L46, L66 and L69 of the human acceptor immunoglobulin is replaced. This does not provide adequate written support for the

narrower subgenus of humanized chicken immunoglobulins wherein at least one residue selected from the group consisting of H78, H93, L66 and L69 is replaced with the corresponding residue of the chicken immunoglobulin, or the variety of subgenera of humanized chicken immunoglobulins defined by a single framework residue, i.e., H78, H93, L66 or L69. There is insufficient written support or description of the subgenus of humanized chicken immunoglobulins wherein residue H78 is replaced with the corresponding residue of the chicken immunoglobulin, the subgenus of humanized chicken immunoglobulins wherein residue H93 is replaced with the corresponding residue of the chicken immunoglobulin, the subgenus of humanized chicken immunoglobulins wherein residue L66 is replaced with the corresponding residue of the chicken immunoglobulin, and the subgenus of humanized chicken immunoglobulins wherein residue L69 is replaced with the corresponding residue of the chicken immunoglobulin and each subgenus is highly variant. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). The written description of the present application does not set forth a representative number of species of humanized chicken immunoglobulins wherein only framework residue H78 is replaced with the corresponding amino acid from the donor chicken immunoglobulin, or wherein only framework residue H93, or wherein only framework

residue L66, or wherein only framework residue L69 is replaced with the corresponding amino acid from the donor chicken immunoglobulin. It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith* 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The instant claims now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the instant claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in the instant claims in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

9. Claims 30 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andris-Widhopf et al (Journal of Immunological Methods, 242:159-181, 2000) and Queen et al (U.S. Patent 5,530,101, issued 6/25/1996, IDS reference A1 filed 1/10/05) Foote et al (Journal of Molecular Biology, 224:487-499, 1992)

Claims 30 and 33 are drawn to a method of producing a humanized chicken immunoglobulin comprising preparing an expression vectors comprising DNA encoding heavy and light chain variable regions each comprising CDRs from a chicken immunoglobulin and human frameworks, transforming host cells with said vectors and culturing the transformed host cells to produce the humanized chicken immunoglobulin and wherein a residue in at least one position selected from H78, H93, L66 and L69 of the human acceptor immunoglobulin framework is replaced with the corresponding amino acid from the donor chicken immunoglobulin and replacing a rare amino acid in the human framework with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid).

Andris-Widhopf et al teach methods for the generation of chimeric chicken immunoglobulins and due to the ability to generate an immune response to highly conserved mammalian antigens that do not otherwise give rise to antibodies in mice and rabbits due to immunotolerance, chickens provide a useful source of clinically relevant antibodies that have human therapeutic potential and the use of single VH and VL genes in chicken immunoglobulins simplifies the use of genetic techniques for antibody engineering as only one set of oligonucleotide primers is needed for each antibody chain (see entire document, particularly abstract, pp. 159-160, 169, 179 and Fig. 1). Andris-Widhopf et al do not specifically teach a method of producing a humanized chicken immunoglobulin comprising preparing expression vectors comprising DNA encoding heavy and light chain variable regions each comprising CDRs from a chicken immunoglobulin and human frameworks, transforming host cells with said vectors and culturing the transformed host cells to produce the humanized chicken immunoglobulin and wherein the humanized chicken immunoglobulin comprises framework residues from the chicken immunoglobulin that are capable of interacting with the CDRs and replacing rare amino acids in the human framework with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) and wherein a residue in at least one position selected from H78, H93, L66 and L69 of the human acceptor immunoglobulin framework is replaced. These deficiencies are made up for in the teachings of Queen et al and Foote et al.

Queen et al teach that while chimeric antibodies have proven somewhat successful in reducing the immunogenicity of nonhuman antibodies in human patients, a significant immunogenicity problem remains and Queen et al teach a method of producing humanized immunoglobulins that are less immunogenic in human patients and better suited for human therapy, said method comprising preparing expression vectors comprising DNA encoding a heavy and light chain variable regions each comprising CDRs from a nonhuman immunoglobulin and human frameworks, transforming host cells with said vectors and culturing said transformed host cells to produce said humanized immunoglobulin and replacing rare amino acids in the human framework with an amino acid that is more common at its position among human

immunoglobulins (i.e., consensus amino acid) (see entire document, particularly col. 1, 14-16 and Table 1 at col. 43).

Foote et al teach that vernier zone framework residues, including residues H78, H93, L66 and L69, may adjust CDR structure and fine-tune the fit to antigen and the vernier zone has obvious consequence for the design of humanized antibodies and should be matched (see entire document, particularly pg. 497 and Table 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method of making a humanized chicken immunoglobulin comprising preparing expression vectors comprising DNA encoding humanized heavy and light chain variable regions comprising CDRs from a chicken immunoglobulin and human frameworks, transforming host cells with said vectors and culturing said transformed host cells to produce said humanized chicken immunoglobulin, wherein at least one human framework residue selected from H78, H93, L66 and L69 is replaced with the corresponding amino acid from the donor chicken immunoglobulin and a rare amino acid in the human frameworks is replaced with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) for therapeutic benefit in human patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to produce a method of making a humanized chicken immunoglobulin comprising preparing expression vectors comprising DNA encoding humanized heavy and light chain variable regions comprising CDRs from a chicken immunoglobulin and human frameworks, transforming host cells with said vectors and culturing said transformed host cells to produce said humanized chicken immunoglobulin, wherein at least one human framework residue selected from H78, H93, L66 and L69 is replaced with the corresponding amino acid from the donor chicken immunoglobulin and replacement of a rare amino acid in the human frameworks with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) for therapeutic benefit in human patients in view of Andris-Widhopf et al and Queen et al and Foote et al because Andris-Widhopf et al teach methods for the generation of chimeric chicken

immunoglobulins and due to the ability to generate an immune response to highly conserved mammalian antigens that do not otherwise give rise to antibodies in mice and rabbits due to immunotolerance, chickens provide a useful source of clinically relevant antibodies that have human therapeutic potential, however, a significant immunogenicity problem remains with chicken antibodies according to Queen and Queen et al teach a method of producing humanized immunoglobulins that are less immunogenic in human patients and better suited for human therapy compared nonhuman and chimeric antibodies, the method comprising preparing expression vectors comprising DNA encoding a heavy and light chain variable regions each comprising CDRs from a nonhuman immunoglobulin and human frameworks, transforming host cells with said vectors and culturing said transformed host cells to produce said humanized immunoglobulin and replacing rare amino acids in the human framework with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) and Foote et al teach that vernier zone framework residues, including residues H78, H93, L66 and L69, may adjust CDR structure and fine-tune the fit to antigen and the vernier zone has obvious consequence for the design of humanized antibodies and should be matched. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated and had a reasonable expectation of success to modify the chimeric chicken immunoglobulin of Andris-Widhopf et al and produce a humanized chicken immunoglobulin according to the method of Queen et al because chickens generate an immune response to highly conserved mammalian antigens that do not otherwise give rise to antibodies in mice and rabbits due to immunotolerance and thus, provide a useful source of clinically relevant antibodies that have human therapeutic potential and the use of single VH and VL genes in chicken immunoglobulins simplifies the use of genetic techniques for antibody engineering as only one set of oligonucleotide primers is needed for each antibody chain and humanized chicken immunoglobulins would overcome the immunogenicity problem that remains with chimeric antibodies. Further, one of ordinary skill in the art would have been motivated to adjust CDR structure and fine-tune the fit to antigen by matching the vernier zone residues including H78, H93,

L66 and L69, which have obvious consequence for the design of humanized antibodies according to Foote et al. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Semaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a method of making a humanized chicken immunoglobulin comprising preparing expression vectors comprising DNA encoding humanized heavy and light chain variable regions comprising CDRs from a chicken immunoglobulin and human frameworks, transforming host cells with said vectors and culturing said transformed host cells to produce said humanized chicken immunoglobulin, wherein at least one human framework residue selected from H78, H93, L66 and L69 is replaced with the corresponding amino acid from the donor chicken immunoglobulin and replacement of a rare amino acid in the human frameworks with an amino acid that is more common at its position among human immunoglobulins (i.e., consensus amino acid) for therapeutic benefit in human patients in view of Andris-Widhopf et al and Queen et al and Foote et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643